Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The title of the application has been changed as required by the Examiner at page 2 of the Official Action.

A new Abstract of Disclosure is submitted in accordance with the Examiner's requirement at page 2 of the Official Action.

Claims 1-9 are present in the application.

The claims are rejected under the judicially created doctrine of obviousness-type double patenting over the claims of the Baltes et al. patent (U.S. 4,525,358).

Applicant respectfully submits that this rejection is unnecessary, and should be made only in a situation where the prior patent is not otherwise available as references against the claims. Here, however, this reference is otherwise available to the Examiner, and the Examiner has applied the reference in rejections set forth on pages 2 to 4 of the Official Action. In order to avoid these rejections, Applicant must establish that the subject matter being claimed in the present application is patentably distinct from the subject matter disclosed in this prior patent. That disclosure includes not only the claims but also the specification of this patent. If Applicant establishes this patentable distinction, he does, of necessity, also overcome the obviousness-type double patenting rejection. On the other hand, if Applicant does not establish this patentable distinction, then, in such case, the double patenting rejection becomes nothing more than another "nail in the coffin". Thus, Applicant respectfully submits that the obviousness-type double patenting rejection is totally unnecessary.

Applicant also respectfully submits that the position advanced by the Examiner in the two full paragraphs spanning pages 6 and 7 of the Official Action is likewise superfluous. All that Applicant can accomplish by complying with the requirement of the Examiner is to avoid these patents as qualifying prior art under 35 U.S.C. §102(f) or (g). Even if Applicant does so, this patent still qualifies as prior art against the present application under the provisions of 35 U.S.C. §102(a) and (b). On the other hand, if Applicant establishes that the instantly claimed subject

matter is patentably different from the subject matter described and/or claimed in this prior patent, he not only overcomes the rejections based upon these patents under 35 U.S.C. §102(a) and (b)/103, but also overcomes any rejection based upon this patent qualifying as prior art under 35 U.S.C. §102(f) and (g). Thus, Applicant respectfully submits that the Examiner's position in this regard is totally unnecessary.

Notwithstanding the foregoing comments, however, and solely in order to avoid a holding of abandonment of this application based upon the statement of the Examiner in the sentence spanning pages 6 and 7 of the Official Action, Applicant hereby states that the invention described and claimed in the Baltes et al. patent was invented prior to the Applicant's invention of the subject matter claimed herein. Further, the Applicant hereby states that at the time he invented the subject matter claimed herein, he was under an obligation to assign his rights to such subject matter to the assignee of the Baltes et al. patent.

With the foregoing comments in mind, it is now possible to proceed to a discussion of the other rejections which the Examiner has set forth in the Official Action, i.e., the rejections set forth at pages 2 to 4 and in the second full paragraph on page 7.

The claims are rejected under 35 U.S.C. §102(b) as being anticipated by Cossement (GB'321) while citing Merck Index and Baltes as supplementary evidence of what Cossement teaches. This ground of rejection is deemed to be untenable and is thus respectfully traversed.

In the first place, while the Examiner attempts to disguise the fact, she is actually impermissibly attempting to combine references in an effort to formulate an anticipation rejection. The teachings of Merck Index and Baltes upon which the Examiner relies are not at all explanatory of what Cossement teaches but are additional teachings which the Examiner improperly attempts to use in formulating the anticipation rejection. Note that both of these "supplementary" references are silent as to isomerism. For this reason alone, the anticipation rejection is untenable and should be withdrawn. Furthermore, substantively the rejection is untenable.

As noted above, the Merck Index and Baltes references are silent as to isomerism.

Turning now to Cossement, it is Applicant's opinion that the relevant disclosure therein is merely declaratory, and does not constitute a clear, unambiguous teaching of the use of a pure cetirizine enantiomer in any form of therapy. In particular, the passage cited by the Examiner states that:

> "...(the relevant compounds)... may exist in levorotatory form, the dextrorotatory form or a mixture of the levorotatory and dextrorotatory forms."
>
> (emphasis added)

It is submitted that this statement amounts to nothing more than a recognition of the optically active nature of compounds described. It certainly does not amount to a clear, unambiguous and enabling teaching to purify any particular enantiomer and use it in therapy.

Moreover, the passage on page 1, line 12-16, simply states that:

> "...cetirizine[,] has recently been introduced as a new medicament for the treatment of allergic syndromes, such as chronic and acute allergic rhinitis, allergic conjunctivitis, puritus, urticaria, etc. ..."

It is submitted that this statement amounts to nothing more than a neutral declaration of the recognized uses of the racemate in the form of a non-exhaustive list. There is absolutely nothing to indicate that this passage should be read in combination with the foregoing references to optically active forms. Thus, it cannot amount to an anticipation of the use of any particular enantiomer in the treatment of any of the diseases listed.

Accordingly, it is submitted that the claims are clearly novel over Cossement with or without the supplementary evidence of Merck and Baltes.

Moreover, and without prejudice to the generality of the foregoing arguments and observations, it is submitted that under no reasonable interpretation can the relevant disclosure of Cossement be considered to amount to a teaching of the selection of the (+) enantiomer specifically. Rather, the reference to the (+) enantiomer occurs in the context of a bland statement of fact ("...the compound may exist...").

Thus, the Examiner's anticipation rejection is unsound and should be withdrawn.

The claims are rejected as being unpatentable, under 35 U.S.C. §103(a), over Cossement, Baltes and Merck Index. This rejection is likewise deemed to be untenable and is respectfully traversed.

Although the existence of the isomers of a compound having an asymmetric carbon atom as such may be obvious, the present invention is based upon the surprising discovery that (+) - cetirizine is a non-competitive antihistamine inhibitor while (-) - cetirizine is a competitive antihistamine inhibitor. Supporting data is set out in the specification and is summarized in the attachment hereto.

This finding led to the recognition that (+) - cetirizine, as a non-competitive inhibitor, has the unexpected advantage of being able to inhibit the effects of histamine even when the latter is present at high local concentrations.

In the absence of this surprising discovery, there would have been no motivation for those skilled in the art to formulate medicaments based on the (+) - cetirizine enantiomer; if anything, those skilled in the art would have been led away from the use of (+) - cetirizine.

Thus, it is submitted that the present invention can on no reasonable grounds be considered to be an obvious extension of the teaching of the prior art.

The same argumentation applies with respect to the Baltes '358 patent.

Thus, the Examiner should reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Finally, the claims are rejected as being anticipated by Gray '183 under 35 U.S.C. §102(e). This ground of rejection is also deemed to be untenable and is respectfully traversed.

It is the Applicant's position that the date of invention in the U.S. for the subject matter being claimed herein predates the effective 102(e) date of the Gray patent. Applicant is presently engaged in assembling the necessary evidence to establish that this is the case. This involves obtaining the permission of a third party to provide the necessary evidence. Applicant is further having difficulty in this regard owing to the age of the evidence and the absence of individuals involved at that time.

The forbearance of the Examiner in this respect is requested and Applicant will continue to work to resolve the matter at the earliest possible date.

The Examiner is requested to reconsider this application in light of the forgoing remarks.

Respectfully submitted,

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September 15, 2004

ATTACHMENT TO RESPONSE

The affinity of (+)- and (-)- cetirizine towards the rat cortex histamine H_1 histamine receptor was determined using the method described by Millan et al. (1990), J. Pharmacol. Exp. Ther., 252(3), pages 1090-1096. This assay involves the competitive binding to the receptor of the compound to be tested and a radioligand (in this case, [^{3}H]mepyramine, a selective antagonist of the receptor). Displacement curves of the binding of [^{3}H]mepyramine were plotted for various concentrations of the compounds to be tested ranging from 10^{-11} to 10^{-4} mole/l, and for a concentration of 4.3×10^{-9} mole/l of [^{3}H]mepyramine (24.8 Ci/mmole from New England Nuclear, Belgium).

Cerebral cortexes from male Sprague-Dawley rats were homogenized in 2 ml per cortex of a 20 mM Tris-HCl buffer (pH7.4) containing 250 mM sucrose. The homogenates were centrifuged at 30,000 g for 30 minutes at 4°C and the centrifugation pellets resuspended in the same fresh buffer and preserved in liquid nitrogen.

To determine binding to the receptor, the samples containing 0.5 mg of cortex membrane protein in 0.5 ml of 50 mM Tris-HCl buffer (pH 7.4) containing 2 mM magnesium chloride are incubated with [^{3}H]mepyramine and the compound to be tested at 25°C for 60 minutes. The bound [^{3}H]mepyramine was separated from the free radioligand by rapid filtration of the sample through a Whatman GF/C filter, previously impregnated for at least 2 hours with a 0.1% solution of polyethyleneimine, in order to reduce the possibility of non-specific binding of the radioligand with other proteins. The residue from the filtration is then washed four times with 2 ml of 50 mM Tris HCl buffer (pH 7.4) and cooled in an ice bath. The radioactivity thereof was then measured using a beta particle Tri-carb 1090 scintillation counter (Canberra-Packard, Belgium). Non-specific binding was estimated in the presence of a 10 µM aqueous solution of cetirizine and represented 10% of [illegible] binding. The IC_{50} values of the compounds tested (concentrations in mole/l necessary to inhibit binding of the radioligand to the receptor by 50%) were determined by analysis of the competitive binding curves and their inhibition constants (K_i) were calculated by means of the Cheng and Prusoff equation (Cheng and Prusoff, Biochem. Pharmacol., 22 (1973), pages 3099-3108).

The values of pK_i (cologarithm of K_i) calculated from K_i (mean value+/-deviation with respect to the mean (n=2)) for (+)-cetirizine and (-)- cetirizine were:

(-)-cetirizine: 7.4 +/- 0.0

(+)-cetirizine: 8.2 +/- 0.0

These results show that (+)-cetirizine has a greater affinity (by factor of about 12) for the rat cortex histamine H_1 receptor.

ANNEXE II

Trachaes of Dunkin-Hartley guinea pigs of both sexes (weight: 250-500 g) were excised and cut into four fragments of three segments of cartilage each. These fragments were immersed in a Krebs-Heinseleit solution at 37°C containing 10^{-7} mole/l of atropine and 10^{-5} mole/l of indomethacin and were stretched with a weight of 1 g. The solution was aerated with a current of oxygen containing 5% carbon dioxide. Each change in tension was recorded with an isometric force indicator K 30 (from Hugo Sachs Elektronik) coupled to an amplifier and a Sanborn 7700 recorder (Hewlett Packard). The preparation (i.e. trachea fragment) so obtained was allowed to stabilize for one hour during which the base line for the tension was readjusted if necessary.

Each preparation was precontracted by the addition of 10^{-4} mole/l of histamine to the medium; the observed contraction was taken as a reference (100%). After washing and stabilization, a cumulative curve showing the effects of histamine, as a function of its concentration (10^{-6}, 10^{-5} and 10^{-4} mole/l) was plotted as a control.

For the same preparation, four further cumulative curves showing the effects of histamine as a function of its concentration were then recorded at four increasing concentrations of each compound to be tested.

The compounds to be tested were incorporated in the medium five minutes before the histamine. Between each measurement, the preparations were washed at least four times with an interval of five minutes between each washing. Each compound was tested on at least 6 trachea fragments. When the last curve was plotted, additional concentrations of 3.2×10^{-4} and 10^{-3} mole/l of histamine were added in order to determine whether the antagonism was competitive or not.

When non-competitive inhibition was observed, pD_2 was calculated (the cologarithm of the concentration of the compound tested which causes a 50% inhibition of the maximum recorded contraction. When competitive inhibition is observed, pA_2 was calculated (the cologarithm of the concentration of the compound tested which requires the histamine dose to be doubled in order to obtain the same contraction effect).

The results were:

Compound	pA_2	pD_2
(-)-cetirizine:	6.6 +/- 0.3	-
(+)-cetirizine:	-	6.3 +/- 0.2

The results reveal a surprising characteristic for the tested enantiomers: one enantiomer ((-)- cetirizine) is a competitive inhibitor, whereas the other ((+)- cetirizine) is a non-competitive inhibitor.